The pharmacological profile of a novel highly potent bisphosphonate, OX14, with reduced bone affinity, is as effective as zoledronic acid at inhibiting bone resorption in normal growing mice and rats and in the treatment of myeloma bone disease in JJN3-NOD/SCID-γ mice

M A Lawson1,2, F H Ebetino3, A Mazur4, A D Chantry1,2, J Paton-Hough1,2, H R Evans1,2, D Lath1,2, M K Tsoumpra1,2, M W Lundy5, R L M Dobson6, M Quijano6, A A Kwaasi7, J E Dunford7, X Duan7, J T Triffitt7, G Jeans6 and R G G Russell1,2,7

1Department of Oncology and Metabolism & 2Melanby Centre for Bone Research, Medical School, University of Sheffield, UK, 3University of Rochester, Rochester, NY, USA, 4TWI Chem LLC, Mason, Ohio, USA, 5Indiana University, Indianapolis, IN, USA, 6Procter & Gamble, Mason, Ohio, USA. 7The Botnar Research Centre, Nuffield Orthopaedic Centre, University of Oxford, UK.

Introduction

Bisphosphonates are widely used in the treatment of clinical disorders characterised by increased bone resorption, including osteoporosis, Paget’s disease and the skeletal complications of malignancy. The antiresorptive potency of the nitrogen-containing bisphosphonates on bone in vivo is now recognised to depend upon two key properties, namely mineral binding affinity and inhibitory activity on farnesyl pyrophosphate synthase (FPPS), and these properties vary independently of each other in individual bisphosphonates. The better understanding of structure activity relationships among the bisphosphonates has enabled us to design a series of novel bisphosphonates with a range of mineral binding properties and antiresorptive potencies. Among these is a highly potent bisphosphonate with reduced bone affinity, namely 1-fluoro-2-(imidazo-[1,2 alpha]pyridin-3-yl)ethyl-bisphosphonate, also known as OX14 (Fig. 1). The aim of this work was to characterise OX14 pharmacologically in relation to other bisphosphonates currently used clinically.

Methods

In vitro evaluation of OX14 compared to other bisphosphonates

The retention and binding of OX14 was compared to alendronate (ALN), zoledronic acid (ZOL), ibandronate (IBN) and risedronate (RIS) on a hydroxyapatite (HAP) column.2 The potential anti-resorptive potency of OX14 was compared to ALN, ZOL, IBN and RIS in a FPPS inhibition assay.2

In vivo evaluation of OX14 compared to other bisphosphonates

In a growing rat model and in a growing mouse model the effects of OX14 on bone binding affinity and bone resorption were compared to other bisphosphonates. The therapeutic effects of OX14 were assessed in the JJN3-NSG murine model of myeloma and compared to ZOL. Groups of female NSG mice (n=8) were injected with 1x10⁶ JJN3 cells and treated with Vehicle, ZOL or OX14 (125 µg/kg sc 2x/wk). Micro-CT analysis was used to measure trabecular bone volume and number of cortical bone lesions. The numbers of osteoclasts on tibial cortico-endosteal surfaces were assessed using standard histomorphometric methods. Tumour burden was assessed in bone marrow flushes of the left femora at the end stage of disease by flow cytometry using an anti-human HLA-ABC-APC antibody.

Results

When compared to ALN, IBN, RIS and ZOL, OX14 was the most potent at inhibiting FPPS in vitro, and had the lowest binding affinity to HAP columns (Fig. 1). When injected into Sprague Dawley growing rats, OX14 was excreted into the urine to a greater extent than other bisphosphonates, indicating lower skeletal retention, and it resulted in increased BMD compared to RIS (Fig. 2).

Conclusions

In summary, OX14 is a new highly potent bisphosphonate with lower bone affinity than other clinically relevant bisphosphonates. This renders OX14 an attractive candidate for clinical development for its potential skeletal or non-skeletal benefits.

Acknowledgements

We like to thank Bloodwise and Procter & Gamble for supporting this work.

